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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,801	09/10/2003	Paolo Gatti	PC23575A	1817

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EXAMINER	
SCHLIENTZ, NATHAN W	

ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/658,801	GATTI, PAOLO	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *107,111,113 and 115-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *107,111,113 and 115-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10 October 2008 has been entered.

Status of Claims

Claims 107, 111, 113 and 115-119 are pending in this application and are examined herein on the merits for patentability. No claim is allowed at this time.

Withdrawn Rejections

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 107, 111, 113 and 115-119 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the claims recite, "a bulk density of at least about 0.50 kg/L (0.60 kg/L and 0.64 kg/L)". However, "at least" implies greater than or equal to a definite value, whereas about 0.50 kg/L encompasses other bulk densities close to 0.50 kg/L. Therefore, it is unclear what definite bulk density value the formulations are greater than or equal to, and thus the scope of the claims are not clearly defined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 107, 111 and 113, 115-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shenoy et al. (WO 01/37820 A2) in view of Franz (US 4,609,675) and Oshlack et al. (US 6,077,533).

Applicant claims:

The instant claims are drawn to a solid formulation comprising 35-45 wt.% of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, 10-86 wt.% diluent (i.e. mannitol), 2-20 wt.% binder (i.e. croscarmellose sodium), 2-20 wt.% disintegrant (i.e. povidone), and 1-10 wt.% lubricant (i.e. magnesium stearate), wherein the formulation has a bulk density of at least about 0.50 kg/L, 0.60 kg/L, or 0.64 kg/L, no more than 55% of the particles have a size less than 250 µm, and it does not comprise a surfactant or a flow enhancer.

Claim 119 is drawn to a solid formulation comprising 15.2 wt.% 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, 72.7 wt.% mannitol, 6 wt.% croscarmellose sodium, 5.1 wt.% povidone and 1 wt.% magnesium stearate, and a bulk density of at least 0.50 kg/L.

Determination of the scope and content of the prior art

(MPEP 2141.01)

With respect to Claim 111, Shenoy et al. teach a formulation comprising 0.01-***10*** wt.% ionizable substituted indolinone, 10-***80*** wt.% diluent, 0-***5*** wt.% binder, ***4***-10 wt.% disintegrant, and ***1***-1.5 wt.% lubricant (pages 92 and 93, Table: "All formulation components") (***emphasis added***).

With respect to Claims 107, 111, 113 and 115-119, Shenoy et al. teach a formulation comprising 15-75 wt.% ionizable substituted indolinone, 5-95 wt.% binder, 4-10 wt.% disintegrant, and 1-1.5 wt.% lubricant (page 96, 2nd Table, "Indolinone + Surfactant + Diluent + Binder + Disintegrant + Lubricant + Flow Enhancer").

Shenoy et al. further teach that 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide is a suitable ionizable substituted indolinone (page 39, compound 80; and pages 158-159, Example 80). Shenoy et al. also teach that the ionizable substituted indolinone contemplated for use are pharmaceutically acceptable salts which do not abrogate the biological activity and properties of the compound (page 60, lines 1-6), wherein the ionizable substituted indolinone is reacted with a molar equivalent of a base solution or an acid solution, such as malic acid (page 65, lines 1-4; page 76, lines 1-3).

Shenoy et al. also teach suitable pharmaceutically acceptable diluents include mannitol (page 73, lines 14-15); suitable pharmaceutically acceptable binders include polyvinylpyrrolidone (i.e. povidone) (page 73, lines 17-18); suitable pharmaceutically acceptable disintegrants include croscarmellose (page 73, lines 19-21); suitable pharmaceutically acceptable lubricants include magnesium stearate (page 73, lines 26-27).

With respect to Claim 113, Shenoy et al. teach that the broadest range of surfactants and flow enhancers encompasses 0 wt.% (pages 92 and 93, Table: "All formulation components"; and page 96, 2nd Table, "Indolinone + Surfactant + Diluent + Binder + Disintegrant + Lubricant + Flow Enhancer").

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Although Shenoy et al. teach 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide as a suitable ionizable substituted indolinone, and the acid solution comprising malic acid, Shenoy et al. do not explicitly teach the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide. However, it is well-known in the art at the time of the instant invention to employ pharmaceutically acceptable salts of compounds in pharmaceutical formulations in order to enhance the solubility of the compound, thus providing greater solubility. Shenoy et al. teach that salts tend to be more soluble in aqueous or other protonic solvents than are corresponding free base forms (page 87, lines 8-12).

Shenoy et al. do not teach the bulk density of their formulations to be at least 0.50 kg/L, at least 0.60 kg/L, or at least 0.64 kg/L, as instantly claimed. However, Franz teaches that drugs with high bulk density values reduce the volume or size of the tablet or capsule needed for a desired dosage per unit (col. 3, ln. 3-6 and 20-21). Franz teaches that high bulk density formulations are adaptable for further processing to make a range of solid dosage unit strength forms in smaller sized compressed tablets or filled capsule forms (col. 5, ln. 8-12). Franz further teaches that high bulk density (at least 0.4 g/ml, untapped, and at least 0.5 g/ml tapped) formulations can be incorporated into tablet and capsule end product pharmaceutical formulations with or without typical

pharmaceutical adjuvants that result in dosage forms having reasonable tablet and capsule size limits that aid in patient acceptance (col. 8, ln. 39-50).

Also, Oshlack et al. teach powder-layered dosage forms wherein the therapeutically effective agents have a bulk density (poured and tapped) from about 0.2 g/ml to about 0.8 g/ml, more preferably from about 0.4 g/ml to about 0.75 g/ml (col. 7, ln. 60 - col. 8, ln. 1), wherein the layered beads are passed through a series of screens to remove undesirable sized beads, such as beads having diameters above 1.19 mm and below 0.84 mm (col. 8, ln. 59-63).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to use the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide in the formulations of Shenoy et al. because Shenoy et al. reasonably teach 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide as a suitable ionizable substituted indolinone and that salts tend to be more soluble in aqueous or other protonic solvents than are corresponding free base forms. It also would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to make the formulations of Shenoy et al. with a bulk density that is high enough to result in dosage forms having reasonable tablet and capsule size limits that aid in patient acceptance, as reasonably taught by

Franz; as well as screening the particles for optimal size, such as between 0.84 and 1.19 mm, as reasonably taught by Oshlack et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's Remarks filed 11 December 2008 have been fully considered but they are not persuasive. Applicants argue on pages 4 and 5 that it would not have been obvious to modify the teachings of Shenoy et al. to select the malate salt of the ionizable substituted indolinone, nor would it have been obvious to select the specific narrow ranges of components in order to produce a composition having improved bulk density and processing properties. Applicants further argue that the comparative examples within the instant specification (paragraphs [0469], [0470], [478] and [0479] of the application publication US 2004/0229930) show that the properties of the formulation such as bulk density are not inherent in the Shenoy et al. disclosure.

The examiner respectfully disagrees. With respect to the selection of the malate salt of the ionizable substituted indolinones, Shenoy et al. clearly teach salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms (pg. 87, ll. 11-12; and pg. 82, ll. 24-25). Shenoy et al. further teach that the ionizable substituted indolinones contemplated for use in their invention are

pharmaceutically acceptable salts (pg. 60, ll. 1-2), and the indolinone is solubilized by combining it with a molar equivalent of a base or an acid solution (pg. 64), such as malic acid (pg. 65, ll. 1-4; pg. 76, ll. 1-3; pg. 79, l. 30 through pg. 80, l. 1; pg. 87, ll. 8-11; and claim 11). Therefore, Shenoy et al. clearly teaches the desire to use the pharmaceutically acceptable salt of the ionizable substituted indolinones, wherein malic acid is one of the preferred acid solutions for solubilizing said indolinones.

With respect to the concentration of the components, Shenoy et al. teach a set of ranges that is suitable for their invention, wherein the ionizable substituted indolinone is present from 5-90%, preferably 1-80%, and most preferably 15-75%, as acknowledged by Applicants (pg. 96, 2nd table). Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art to use the ionizable substituted indolinone at 35 to 45 wt.% as instantly claimed.

Applicants further argue on pages 5-6 that the bulk density is not inherently above 0.50 kg/L. However, the examiner has provided arguments above that show that it was *prima facie* obvious for one of ordinary skill in the art to choose bulk density of at least 0.50 g/ml in order to reduce tablet or capsule size and increase patient compliance, as reasonably taught by Franz.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is

(571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616